MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: October 12, 1999

From: Michael F. Johnston, R.Ph., Postmarketing Safety Evaluator
Division of Drug Risk Evaluation I, HFD-430

Through: Peter K. Honig, M.D., M.P.H., Director *(Signed 10/12/99)*
Division of Drug Risk Evaluation I, HFD-430

To: Charles J. Ganley, M.D., Director
Division of Over-The-Counter Drug Products, HFD-560

Subject: Consult
Drug : Over-The-Counter Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
Reaction: Renal Failure at OTC Dosing Levels

EXECUTIVE SUMMARY

In response to a Division of Over-The-Counter Drug Products (DOTCDP) consult, we reviewed 126 cases of renal failure associated with the use of ibuprofen, naproxen, and ketoprofen occurring with OTC-approved dosages. A sufficient number of renal failure cases were reported with OTC dosages, especially with ibuprofen and naproxen, to warrant addition of wording to the OTC labeling concerning potential renal problems. Minimally, it is recommended that patients with pre-existing renal problems be informed of the risk and to consult with their physician prior to use.

INTRODUCTION

We received a consult request dated August 3, 1999 for a review of the Adverse Event Reporting System (AERS) for renal failure cases reported with the three OTC NSAID products (ibuprofen, naproxen, and ketoprofen) when used at OTC dosages. A telephone conversation shortly thereafter with Rosemarie Neuner, M.D. of the DOTCDP related that the National Kidney Foundation has requested that the FDA review renal failure reports for these products. The ultimate goal would be to place warnings related to renal failure in the labeling of OTC NSAID products prior to the upcoming switch of ibuprofen to monograph status. Although renal failure is well documented in the literature and in the labeling of prescription NSAIDs, the current labeling for the OTC NSAIDs does not refer to this adverse event. Dr. Neuner's telephone conversation also requested that we not confound cases in our review unless it could be shown that the NSAID clearly did not cause or contribute to the reported renal failure. Accordingly, we reviewed all cases in which the OTC NSAID may have played a contributory role to the reported renal failure.

DRUG INFORMATION and LABELING

Current labeling and packaging for these three OTC does not mention any renal events.

Ibuprofen, naproxen, and ketoprofen prescription drug products all contain extensive information in their *Precautions* and *Adverse Reactions* sections related to renal effects, including warnings about using these medications in patients with creatinine clearances of less than 20 ml/minute. Other terms mentioned include interstitial nephritis, glomerular nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, and impairment of renal function.

Prescription NSAID class labeling also refers to a second form of renal toxicity leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal blood flow. The labeling defines patients at the greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.

MEDICAL LITERATURE SUMMARY

In an August 27, 1999 Email, Dr. Neuner related that she had already requested a literature search which produced mostly articles on renal failure occurring at prescription dosages. We will not review the literature but literature reports of OTC use submitted to AERS are included in the findings below.

DRUG USAGE

Information on all NSAID usage was provided to Dr. Neuner on August 16, 1999 by OPDRA's Extramural Program staff and is not repeated in this document.

SELECTION OF CASE SERIES

The goal of this search was to find cases of renal failure, which have occurred during the time period that these products have been available as non-prescription drugs and appeared to occur at OTC dosages. The following date parameters, based upon the OTC approval date listed below, were used:

Ibuprofen	OTC Approval Date: 5/18/84
Naproxen	OTC Approval Date: 1/11/94
Ketoprofen	OTC Approval Date: 10/5/95

Checking for reports submitted after the above dates, an AERS search on August 10, 1999 using the preferred terms acute renal failure, chronic renal failure, and renal failure (NOS) produced the following results:

Search / Drug	Ibuprofen	Naproxen	Ketoprofen
Total Reports Since OTC Approval Date	13,141	10,794	2,000
Total Renal Failure Reports (Acute, Chronic, NOS)	349	80	42
Cases Remaining – Adult (>16 years) (after removal of Rx dosages, overdoses, duplicates)	80	26	1
Cases Remaining – Pediatric (≤16 years) (after removal of Rx dosages, overdoses, and duplicates)	14	0	0

We reviewed all the above cases of renal failure to identify cases with OTC dosage range only.

The accuracy of both dosage and duration of therapy values reported prior to renal failure may be tainted by the "as needed" nature of NSAID use. In many cases of "as needed" dosing, the daily amount of NSAID reported may actually have been less than that listed on the report.

In each case series, the best effort was made to only retain cases in which it was known that either OTC dosages (with either the OTC or Rx product) and/or an OTC NSAID product played a role in the adverse reaction. Although information is reported about pre-existing conditions (hypertension, renal problems, etc.), these cases are not excluded since, even if underlying disease is involved in the renal failure, the NSAID may have played a contributory role in the renal failure.

Five cases were also found in which patients were using a combination of the above OTC NSAIDs. Each of the above case series and the NSAID combination therapy case series will be reviewed separately below.

Ibuprofen – Adult (> 16 Years Old) (80 Cases):

OTC Approval Date: May 18, 1984
OTC Dosage: 200 mg every 4-6 hours up to a maximum of 1200 mg every 24 hours

Ibuprofen /Renal Failure (> 16 YO) at OTC Dosages (n = 80)			
Year Reported	1985: 1 1986: 1 1987: 2 1988: 7 1989: 4	1990: 3 1991: 4 1992: 4 1993: 9 1994: 6	1995: 2 1996: 9 1997: 5 1998: 6 1999: 11
Age	17-20: 6 21-30: 5 31-40: 7 41-50: 15	51-60: 11 61-70 7 71-80: 14 81-90: 6	Mean: 53.5 Range: 17-85
Gender	Male: 44	Female: 34	Unknown: 2
Product Used	Rx: 32	OTC: 47	Unknown: 1
Report Source	Domestic: 63	Foreign: 14	Literature: 6
Daily Dosage	200 mg: 3 400 mg: 7 600 mg: 10	800 mg: 8 1200 mg: 30 Unknown: 22	
Duration of Therapy	< 1 Day: 7 1-5 Days: 9	6-30 Days: 19 > 30 Days: 14	Unknown: 31

Outcomes Reported	Hospitalized:	56	Recovered:	12
	Deaths:	9	Treatment/Intervention Reqd:	17
	Life Threatening:	8	Dialysis Required:	9
			Severe / Permanent Disability:	9
Dechallenge	Positive: 37		Negative: 12	
Concomitant Disease History Reported	Hypertension:	16	Cancer:	3
	Renal Insuff:	8	Rhabdomyolysis	3
	Diabetes:	7	Hepatic:	2
	Other Cardiac:	8	Lupus:	1
	COPD	6	HIV:	1
	Rheum. Arthritis:	3	Hyperkalemia:	1
	Alcoholism:	3	Hyponatremia:	1
Concomitant Drugs Reported	Diuretics:	15	Digoxin:	4
	Other NSAIDs:	7	Coumadin:	4
	Ca Channel Blockers:	6	Methyldopa:	3
	ACE Inhibitors:	5	Recent EtOH:	3
			Aminoglycosides:	1

In these 80 cases, renal failure was reported slightly more in males than females (44 vs. 34). Hypertension (16), pre-existing renal insufficiency problems (8), diabetes (7), and other cardiac (8) were the most common concurrent diseases reported and 15 of the patients were reported to be taking diuretics prior to the renal failure. These might predispose the population at risk to renal failure development as expected. The most common preliminary symptoms reported in these renal failure patients were: malaise/weakness (6), fever (5), hematuria (4), hypotension (4), nausea/vomiting (4), back pain (4), abdominal pain (4), and dehydration (3). During case reviews it was noted that in five cases, the patient's renal failure was misdiagnosed initially as pregnancy, acute abdomen, or infections. As would be expected, 56 patients noted that hospitalization was required due to the serious nature of their renal failure. It is possible the severity of the renal failure was linked to the difficulty in diagnosing renal failure from clinical symptoms without the availability of laboratory values. Overall, demographics for this case series show ibuprofen-induced renal failure occurring mostly in elderly patients taking cardiac-related medications concomitantly, and within one month of starting higher OTC dosages.

Ibuprofen-induced renal failure was considered at least part of the cause of death in five of the nine deaths. The reported cause of death in these nine cases can be seen in the following table:

Cause of Death (Adult) with Ibuprofen in Reported Renal Failure Cases (n = 9)

Case #	Age	Gender	Reported Cause of Death
1.	79	F	Renal Failure with Sepsis
2.	Unk	M	Pneumonia and disseminated aspergillosois,
3.	38	M	Renal Failure (acute) / Hepatic Failure Hepatitis due to blood transfusion ?
4.	67	M	Lung Cancer, renal failure
5.	48	F	Hepatorenal syndrome →Multisystem Failure Hepatic Failure due to Alcoholism
6.	85	M	Renal Failure / Pneumonia
7.	66	M	GI Bleeding / Septic Shock
8.	54	F	Renal Failure
9.	58	M	Perforated Ulcer / Acute Abdomen

The death cases summarized below show the complex nature of these patients and how ibuprofen may have contributed to the death but is very difficult to consider it as a sole (or even primary cause) of the death.

(FDA #448304, 1986) A 79 year-old female complaining of shoulder pain was treated in the ER with ibuprofen, meperidine, and hydroxyzine. After five days of ibuprofen (reported as 600 mg daily) therapy, the patient returned to the ER complaining of back pain with radiation to shoulder. The patient was hospitalized with a diagnosed of acute renal failure and sepsis. During hospitalization, the patient developed progressive metabolic acidosis and then died of cardiac arrest three days after admission. Three years before this shoulder injury, the patient had taken ibuprofen (1200 mg daily) for 33 weeks without reported problems. The patient's medical history included chronic tonsillitis, carpal tunnel syndrome degenerative arthritic spine, hypertension, and a gall bladder problem.

(FDA #701553, 1990) A 38 year-old male died of hepatitis and acute renal failure two weeks after heart valve replacement surgery due to bacterial endocarditis. The patient had been taking ibuprofen (1200 mg daily) for two weeks. The patient also reportedly was treated with fresh frozen plasma and whole blood during the surgical procedure.

(FDA #1615739, 1995) An 85 year-old male while hospitalized for a broken ankle and pneumonia, developed renal failure and died. This report was related to a legal inquiry made by the physician-expert witness in a lawsuit. The wheelchair-bound patient was struck by an automobile in the nursing home parking resulting in a fractured left humerus. The patient was started on 400 mg of ibuprofen three times a day for ten days. After about two weeks the patient developed worsening fever and dyspnea and was hospitalized for pneumonia. Laboratory values noted worsening renal function. The reporting physician blamed renal failure upon dehydration, myoglobin release, and the use of ibuprofen.

(FDA #3275656-X-00-01, 1999) A 54 year-old female developed acute renal failure and anuria and died after taking ibuprofen (800 mg daily) for four days. Other medications taken during the time of hospitalization included Flagyl, Cipro, acetaminophen, and a single dose (240 mg) of gentamicin. Although medical history was unknown, the patient's chronic medications included furosemide 80 mg daily, spironolactone 200 mg daily, and cimetidine 800 mg daily. The reporter listed ibuprofen as the primary suspect drug.

Ibuprofen – Pediatric ($\leq$ 16 Years Old) (14 Cases)

The demographics of pediatric renal failure patients is as follows:

Ibuprofen /Renal Failure (≤ 16 YO) At OTC Dosages (n = 14)			
Year Reported	1989: 2 1990: 1 1994: 1	1995: 2 1997: 3 1998: 2	1999: 3
Age	1 - 2: 3 3 - 5: 3	5 - 10: 4 10 - 16: 4	Mean: 6.9 Range: 1 - 15
Gender	Male: 8	Female: 6	
Product Reported	OTC: 14		
Report Source	Domestic: 6	Foreign: 4	Literature: 4
Daily Dosage	100 mg: 2 200 mg: 2	400 mg: 4 600 mg: 2	Unknown: 4
Duration of Therapy	≤ 1 Day: 3 2 - 7 Days: 4	> 7 Days: 2 Unknown: 5	
Outcomes Reported	Hospitalized: 14 Permanent Disabil.: 1 Treatment Needed: 1	Treatment Required: 1 Recovered: 2	
Dechallenge	Positive: 9	Negative: 2	
Reason for Use	Orthopedic: 3 Flu Symptoms: 3	UTI: 1 Headache 1	
Concomitant Drugs Reported	Antibiotics: 4	ACE Inhibitors: 1	

In all 14 cases, ibuprofen is either associated with the reported renal failure or may have played a contributory role. All of the pediatric patients used an OTC product. In eight of the 14 cases, it was Children's Advil Suspension while the other six cases had used the ibuprofen 200 mg tablets. Reported duration of therapy, as might be expected due to more limited length of childhood diseases, was shorter (usually less than seven days) than in the adult patients. Symptoms preceding the renal failure diagnosis included vomiting (4), fever (2), and hematuria. There were no reports of abdominal or back pain as were seen in the adult ibuprofen patients. The case review noted the diagnostic difficulty of separating the renal failure symptoms from the symptoms of the injury or illness being treated (either orthopedic, bacterial or viral infection). Although there were no deaths reported in the ibuprofen pediatric patients, all patients (14) required hospitalization. In the four cases where it could be determined, hospitalization was reported to be for three (3 cases) and four weeks (1 case). In this pediatric case series, ibuprofen was primarily prescribed for minor orthopedic and minor childhood diseases and the patients did not have significant underlying disease (i.e. cardiovascular) as seen in the adult cases.

The following cases are summarized as examples of the pediatric cases:

(FDA #637834, 1987, Foreign) A 10 year-old male was hospitalized due to head trauma (from assault). Upon admission, the patient was conscious, tachycardic, BP normal, with neurological and other clinical exams showing normal results. One unit of blood was transfused and ibuprofen was prescribed for headache (200 mg every eight hours). Five days later the patient developed worsening edema, oliguria, and became confused. Twenty-four hours later, seizures occurred and the patient was hospitalized in a coma and was grossly edematous. The patient was diagnosed with acute non-oliguric renal failure. The ibuprofen was stopped, and the patient given mannitol (for cerebral edema), and "supportive treatment for renal failure." Over the following 48

hours, the patient regained consciousness and urine output increased. After three weeks hospitalization, the patient was discharged with normal serum urea and creatinine values. A renal biopsy was not done due to recovery and follow-up on the patient showed the patient doing well with normal urinalysis and serum biochemistry.

(FDA #3002241-7-00, 1997, US) A 7 year-old male was hospitalized due to asthenia, nausea, and renal failure (diagnosed by "blood test") after taking Children's Motrin Oral Suspension for two days (4 –one teaspoonful (100 mg) doses total). The child was referred to a renal center where IV fluids, peritoneal dialysis and antibiotics were administered. After a one-month hospitalization, the patient recovered and was discharged with a diagnosis of ibuprofen-induced renal failure. Reporter also noted that patient had "asymptomatic strep virus" that contributed in some way. One day after discharge, patient was rehospitalized for five days due to UTI with anemia.

Naproxen (26 Cases)

OTC Approval Date: January 11, 1994
OTC Dosage: 200 mg every 8-12 hours up to a maximum of 600 mg every 24 hours.
Note: The 220 mg naproxen products (Aleve) delivers 200 mg naproxen

The demographics of these 26 cases were as follows:

Naproxen /Renal Failure (Adult) at OTC Dosages (n = 26)			
Year Reported	1994: 3 1995: 3	1996: 9 1997: 5	1998: 3 1999: 3
Age	17-20: 1 21-30: 1 31-40: 2 41-50: 4	51-60: 4 61-70: 4 71-80: 5 81-90: 3	Mean: 58.2 Range: 19 - 85
Gender	Male: 11	Female: 15	
Rx or OTC Product Reported	Rx: 7	OTC: 19	
Report Source	Domestic: 25	Foreign: 1	
Daily Dosage	≤ 400 mg: 9	> 400 - 600 mg: 6	Unknown: 11
Duration of Therapy	< 1 Day: 5 2 - 5 Days: 4	6-10 Days: 2 > 10 Days: 5	Unknown: 10
Outcomes Reported	Hospitalized: 25 Treatment Reqd: 17 Life Threatening: 3	Deaths: 3 Dialysis Required: 4	
Dechallenge	Positive: 10	Negative: 5	
Concomitant Disease History Reported	Hypertension: 5 Renal Insuff. 5 Rheum. Arthritis: 5 Diabetes 3 COPD 3	Alcoholism: 2 Other Cardiac 2 Cancer 2 Lupus 1 Rhabodmyolysis: 1	
Concomitant Drugs Reported	Diuretics: 6 Antibiotics 5	C_a Channel Blockers: 4 Other NSAIDS: 2	

The average patient age was slightly older in the naproxen patients than with ibuprofen (58.2 vs. 53.5). As seen with ibuprofen, hypertension (5), renal insufficiency (5), and diabetes (3) were the

most common reported concomitant diseases (besides the disease being treated with the NSAID). The duration of therapy prior to diagnosis was shorter than with ibuprofen with most cases occurring in less ten days and the dosage was often less than the maximum OTC dosage. Symptoms seen in renal failure cases prior to diagnosis included nausea/vomiting (8), dehydration (5), diarrhea (3), and abdominal pain (2). As with the other NSAIDs, it can be difficult to distinguish the underlying problem being treated (various types of pain) from the onset of renal failure. Almost all (25/26) of the naproxen renal failure patients reported requiring hospitalization.

There were three reported naproxen deaths in the renal failure cases that were attributed to the following causes:

Cause of Death (Adult) with Naproxen in Reported Renal Failure Cases (n = 3)

Case #	Age	Gender	Reported Cause of Death
1.	39	M	Multisystem Organ Failure, Renal failure due to long-term lupus.
2.	52	M	Rhabdomyolysis-induced renal failure, sepsis, malignant lymphoma
3.	74	M	Upper GI Bleed due to naproxen, (alcoholism history)

None of the cases implicate naproxen as a sole cause of death but the contributory role of the naproxen has to be considered.

The following are representative of the naproxen cases reported:

(FDA #1541940, 1994) A 39 year old male developed multi-system organ failure and died after using naproxen (Aleve 220 mg tablets) for "aches and pains" due to pneumonia. On admission, the patient was experiencing nose and GI bleeding. Lab values noted increased serum creatinine and decreased platelets and the patient was transferred to medical center in renal and hepatic failure. After treatment with Cytoxan and prednisone, the patient improved, and was discharged with continuing renal failure and thrombocytopenia. The patient was readmitted and died of multisystem organ failure. Medical history included SLE since the teen years (with long remission periods), and seizures. Valproic acid was blamed for elevated liver enzymes seen in reported hepatic failure. Final reported cause of death was renal failure associated with long-term SLE.

(FDA #1703847, 1995) A 64 year-old female was hospitalized due to nausea and vomiting after taking approximately twelve Aleve 220 mg tablets. The patient had been unable to keep down fluids for the week prior to admission. Upon hospitalization, serum creatinine was 13.1 and BUN 127. During the ten day hospitalization, the patient was catheterized, dialyzed, and squamous cell carcinoma of the cervix was found. Renal biopsy noted broad areas of eosinophilic , lymphocytic, and plasmocytic infiltration consistent with hypersensitivity to naproxen. Naproxen was discontinued and prednisone started. Anuria resolved and the patient was discharged ten days later on continuing dialysis, prednisone and famotidine. Follow-up labs eight days after

discharge noted a serum creatinine of 1.8 and BUN 45. Renal function continued to normalize, prednisone was tapered and discontinued, and famotidine and dialysis were also discontinued. The renal failure was considered related to naproxen therapy.

Ketoprofen (1 Case)

OTC Approval Date: October 5, 1995
OTC Dosage: 12.5 mg every 4-6 hours up to a maximum of 75 mg every 24 hours.

Only one case of renal failure was reported with ketoprofen at OTC dosages and the cases is summarized as follows:

(FDA #1960790, Direct Report, 1997) A 28 year-old male was hospitalized due to "loss of kidney function" discovered during a regular physician visit. The patient was taking two tablets three times a day (75 mg daily dosage) for 3-4 weeks of the OTC product, Orudis KT. The product had been self-initiated for headache and muscle ache. Medical history included renal cancer and previous removal of the left kidney.

This report contains limited clinical information for a patient with significant pre-existing renal problems. It is not possible to determine the role that ketoprofen played in this event.

Combination Therapy Using Two of the OTC NSAIDS (5 Cases)

Five renal failure cases were reported in which the patient had taken more than one of the OTC NSAIDS. Each of these cases were reviewed and the demographics were as follows:

Combination OTC NSAIDs /Renal Failure At OTC Dosage Ranges (n = 5)

Year Reported	1994: 1 1997: 1 1996: 1 1999: 2
Age	17, 68, 70, 67 Mean: 55.5 Range: 17 – 67 Unknown: 1
Gender	Male: 1 Female: 3 Unknown: 1
Rx or OTC Product Reported	Both Products OTC: 1 Mixed OTC/Rx: 3 Both Products Rx: 1
Report Source	Domestic: 5
Products Used	Ibuprofen / Naproxen: 4 cases Naproxen / Ketoprofen 1 case
Duration of Therapy	< 1 Week: 2 1 week - 1 month: 2 Unknown: 31
Outcomes Reported	Hospitalized: 3 Dialysis Required: 1
Dechallenge	Positive: 1 Negative: 0
Concomitant Disease History Reported	Rheumatoid Arthritis: 2 Hepatitis: 1 COPD: 2
Concomitant Drugs Reported	Diuretics: 1 Antibiotics: 1 Ca. Channel Blockers: 1

Patient age was in the range of those seen with ibuprofen and naproxen. Other demographics do not note any patterns or notable information.

There was one death reported in the NSAID combination group. This death report is summarized as follows:

> **(FDA #3243548-8-00-01, Direct Rpt, 1999)** A 67 year-old female died of cardiac arrest after a two-day hospitalization due secondary complications of renal failure, hyperkalemia, long-term COPD, and pulmonary hypertension. Medical history included morbid obesity, long-term smoker (1 pack/day), hypertension, arthritis, musculoskeletal pain, and COPD. Medications listed were Aleve, ketoprofen 200 mg, Dyazide, Atrovent, K-Dur, theophylline, Flovent, albuterol, atenolol, amlodipine, and home oxygen. Prior to death several emergency treatments (kayexalate, antibiotics, dialysis, pressors, Cardizem) were tried unsuccessfully.

The twice-daily Aleve therapy and the ketoprofen could have contributed to the renal failure and death but this is a complex medical patient with several other major factors contributing to the patient's demise.

DISCUSSION / RECOMMENDATION

In all 126 cases, one or more of the OTC NSAIDs were associated with renal failure, either as the primary cause or possibly as a contributory cause. In a few cases, it might be considered as the sole causative agent but this is difficult to determine due to the limited clinical information reported in OTC reports and due to the "as needed" nature of drug usage by the patient. The NSAID must also be considered as potentially contributing to the renal failure condition in most of the cases. Overall for all renal failure cases reviewed here, the average age was 54.8. Although more commonly reported with the upper ranges of the OTC dosages, cases also were reported with single dosages and with dosages in the lower OTC range. In the reports, two mechanisms are reported for the NSAID's renal failure involvement. First, bleeding and/or nausea and vomiting due to NSAID gastrointestinal effects, can result in hypovolemia, dehydration, and shock with resulting renal impairment. Another mechanism noted was direct renal hypersensitivity to the NSAID. At least 99 (of 126) renal failure cases reported hospitalization as an outcome.

The ibuprofen pediatric case series provided renal failure cases which occurred within a shorter time-frame (mostly within less that seven days) and in patients without the predisposing factors found in the adult population (cardiovascular problems, renal insufficiency, etc.)

Although most cases were diagnosed from laboratory values, a mixture of symptoms were seen in these patients prior to diagnosis and hospitalization. Among the symptoms seen were back and abdominal pain, hematuria, malaise/weakness, fever, hypotension, nausea/vomiting, diarrhea, and dehydration. In some cases, the diagnosis was initially missed, leading to delay in hospitalization. The overlap of symptoms of renal failure vs. the symptoms being treated with the NSAID could possibly lead the patient to take more NSAID as pain (abdominal and/or back) worsens, hence, delaying the renal failure diagnosis and possibly the outcome.

Signed 10/1/99
Michael F. Johnston, R.Ph.
Safety Evaluator

Concur:

Signed
Min Chen, R.Ph., M.S.
Team Leader